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INVITED RESEARCH HIGHLIGHT

Management of localized prostate cancer: the pendulum swings (back to the middle)

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Herein, we discuss 18-year follow-up data from the Scandinavian Prostate Cancer Group-4 (SPCG-4) trial, a randomized study comparing observation and radical prostatectomy (RP) in patients with localized prostate cancer. The results of this study are contrasted with another study employing a similar randomization, the Prostate Cancer Intervention Versus Observation Trial (PIVOT). We highlight several key differences in study eligibility and enrollment that may account for distinct results, and describe how these datasets impact the complex landscape of therapy for localized prostate cancer.

Current guidelines for the management of localized prostate cancer leave much latitude to the treating physician. For instance, in the setting of low-risk disease (clinical stage T1–T2a, Gleason score ≤ 6 and prostate-specific antigen (PSA) ≤ 10 ng ml⁻¹), The National Comprehensive Cancer network (NCCN) guidelines offer active surveillance, radiotherapy, and prostatectomy as potential options for patients with a reasonable (≥ 10 years) life expectancy.¹ Admittedly, there is little prospective data juxtaposing radiotherapy and prostatectomy – prior attempts at randomizing patients to external beam radiation or surgery were plagued by poor accrual.² Furthermore, well-conducted cohort analyses (such as the Prostate Cancer Outcomes Study) show few substantial differences in long-term functional outcomes with these approaches.³

More data is available to compare watchful waiting with RP from two trials conducted

before and after the advent of PSA screening. The SPCG-4 trial was conducted between 1989 and 1999, with only 5.2% of cancers detected by PSA.⁴ On the other hand, the PIVOT study, conducted between 1994 and 2002, had 75% of cases detected by PSA screening.⁵ The impact of PSA screening in these trials cannot be emphasized strongly enough – it is estimated that PSA screening is associated with a diagnostic lead time of approximately 12 years.⁶

Recently, Bill-Axelsson *et al.*⁴ have reported updates to the SPCG-4 trial. In this study, 695 patients with localized disease and a PSA of <50 ng ml⁻¹ were randomized to receive either watchful waiting or RP. The mean age was 65, 11.7% of men had stage T1c disease, and 71.8% of men had stage T2 disease. It should be noted that T1c tumors were only included after 1994. Three primary endpoints were explored in SPCG-4: (1) death from any cause, (2) prostate-cancer related death, and (3) risk of metastases to bone, outside the pelvic area, or both.⁴ A total of 349 patients were randomized in each group without significant differences in clinical characteristics between the two arms (age, baseline PSA, tumor stage, etc). Modes of prostate cancer detection were also similar between arms. Notably, the majority were diagnosed based on symptoms (43%) or an abnormal rectal exam (25%).

With the recent report, at 18 years of follow-up, the incidence of death was significantly lower in the RP group when compared to the watchful waiting group (56.1% vs 68.9%; hazard ratio (HR) = 0.71, 95% confidence interval (CI) = 0.59–0.86; $P < 0.001$).⁴ Prostate cancer-related deaths were also lower in the RP group (17.7% vs 27.7%; HR = 0.56, 95% CI = 0.41–0.77; $P = 0.001$). In parallel with these trends, the rate of distant metastasis was lower in the RP group (26.1%

vs 38.3%; HR = 0.57, 95% CI = 0.44–0.75; $P < 0.001$). Amongst patients with low-risk disease (defined as a PSA <10 ng ml⁻¹ and Gleason <7), there was a significant reduction in both all-cause mortality and distant recurrence with RP and a nonsignificant trend towards reduction in prostate-cancer related mortality. There was no improvement in any of the three primary endpoints amongst patients with high-risk disease, defined as a PSA >20 ng ml⁻¹ or Gleason score >7 . In contrast, the intermediate-risk group had significantly improved outcomes among patients receiving prostatectomy for all of these endpoints. For men age >65 , there were no differences between cancer-specific survival or overall survival but the rate of metastatic disease was lower in the surgical group. For men under age 65, all endpoints favored surgery suggesting that age might affect the efficacy of RP.

The results of SPCG-4 have been complemented by the recently published PIVOT study.⁵ Entry criteria in PIVOT were similar to those in SPCG-4; however the patient populations were distinct given that most men (75%) had PSA testing that prompted the diagnosis of cancer. The median mean age was 67%, 50.3% of the men had stage T1c disease and 37.2% had stage T2 disease. A total of 731 patients were randomized to receive either RP or observation. At a median follow-up of 10 years, all-cause mortality was 47% in the prostatectomy group when compared to 49.9% in the watchful waiting group (HR = 0.88, 95% CI = 0.71–1.08; $P = 0.22$) without differences among age groups (younger than 65 or 65 and above). RP was associated with a lower rate of prostate cancer mortality among patients with intermediate prostate cancer and those with a serum PSA of >10 ng ml⁻¹; however, there was no benefit in low-risk patients.

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High-risk patients treated with surgery had a strong trend toward improvement in death from prostate cancer (HR = 0.4, 95% CI = 0.16–1.00), but this subset was too underpowered to be conclusive.

What can account for the differing results of SPCG-4 and PIVOT? Life expectancy and stage at diagnosis were clearly distinct between these two trials. At 12 years in the PIVOT trial, 40.9% of men assigned to RP and 43.9% of those assigned to observation had died. The 12-year mortality rate estimated from the SPCG-4 trial indicate that overall mortality was approximately 32% in men randomized to surgery and approximately 39% in men randomized to observation. This, taken with a larger portion of T1c patients (50.3% vs 11.7%), suggests that men in the PIVOT trial had both a shorter life expectancy and earlier stage disease. Taking these factors into consideration, it will be difficult for PIVOT to demonstrate a significant benefit with surgery in terms of cancer-related death.

With recommendations from the US Preventative Services Task Force and other groups shifting away from blanket PSA screening, it is possible that fewer stage T1c tumors will be detected in the modern era.⁷ Another key difference between SPCG-4 and PIVOT is the degree of follow-up in the studies (18 years and 10 years, respectively). In SPCG-4, the difference in mortality between treatment arms increased steadily throughout the duration of follow-up and it is possible that additional follow-up with PIVOT will alter the outcomes for some subsets.

Importantly, neither study formally evaluates active surveillance. By most current

definitions, active surveillance would employ potentially curative therapies in a subset of patients randomized to observation. What constitutes optimal surveillance strategies is not yet clear but many schemas utilize serial biopsies. Although serial biopsy may have a negative impact on morbidity (through sequelae such as pain and infection), it may also reveal higher grade and higher stage tumors, leading to earlier definitive management. The ambitious ProtecT study in the UK randomized patients to active surveillance, prostatectomy or radiation therapy.⁸ The study will require years of follow-up to provide clinically useful results, so until that time, urologists, medical oncologists and radiation oncologists will continue to provide counsel to patients with localized prostate cancer without high-level evidence for a single approach. A concerning possibility is that financial incentives may potentially drive therapeutic decision-making in this setting. Supporting this notion is a recent review of Medicare claims for intensity-modulated radiation therapy.⁹ The report suggested an alarming rise in self-referrals from urologists in private practice, in contrast to no rise in use amongst NCCN cancer centers. The implications of this are extremely unsettling, and underscore the need to resolve the debate on optimal treatment of localized prostate cancer. Until this occurs, clinicians will be guided by conflicting data, anecdotal experiences and (perhaps of greatest concern) financial incentives.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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